

Attachment F

October 4, 2004

To: Steve Thacker

From: Melinda Wharton

Re: Mokdad AH et al. Actual causes of death, JAMA 2004;291:1238-1245

1. The intent of the authors was to update a previously published paper -- McGinnis JM, Foege WH, Actual causes of death in the United States, JAMA 1993;270:2207-2212 -- and to provide a "30,000 foot view" of potential impact of prevention on mortality in the United States. Such an overview could provide a powerful message on the importance of prevention and was a reasonable task for the authors to undertake.
2. The approach taken has proven controversial in part because individual subject matter experts feel that the methodology utilized was not optimal. This may be true, but the authors generally utilized the methodology of the previous paper -- a reasonable approach given their objective. The authors did employ the methodology of Allison et al (JAMA 1999) to estimate mortality attributable to poor diet and physical inactivity, an approach published since the original McGinnis and Foege paper.
3. Since publication of the Mokdad et al paper, it has been pointed out that approach for calculation of mortality attributable to obesity was calculated using the formula for attributable fraction based on unadjusted relative risks instead of adjusted relative risks. While recent publications have addressed this limitation of the Allison approach (e.g., Flegal et al, Am J Epidemiol 2004), no letters to the editor were written to JAMA at the time of publication addressing this issue that would have flagged this as a methodological problem of the paper. Therefore it is understandable -- although not optimal -- that the authors employed the method used in Allison's published paper.
4. A small number of calculation errors have been identified post-publication. The authors intend to report these as errata, which is appropriate and sufficient.
5. The paper appears to have been cleared in formal compliance with CDC clearance policy, although some CIOs felt that their concerns were not adequately addressed by the authors in the clearance process. However, it appears that the existence of residual concerns was not clearly conveyed to the authors of the paper prior to publication. This is unfortunate but without clear communication it is hard to know how the authors could have known that these concerns still existed. Because cross-clearance is a responsibility of

CIO Associate Directors of Science, this issue and its implications should be addressed by the Excellence in Science Committee.

6. Although the broad overview that the authors wished to provide is a reasonable objective, it is apparent that there are serious methodological concerns on the part of some subject matter experts. There are valid concerns about the methodology employed which should be addressed in an appropriate forum, with an exploration of available methodological approaches involving relevant subject matter experts.
7. While beyond the scope of the charge to this group, I am impressed by the level of concern expressed by some CDC staff. At least two underlying factors are likely to have contributed to the concerns expressed about this paper:
  - a. A small group of mostly CIO-level and above authors (including the CDC Director) weighed in on an area that has been a focus of research careers for some CDC scientists. It is not surprising that this led to some concerns but (going back to point 1 above) this paper was a reasonable exercise for policy-level scientists to undertake. Perhaps in the future similar concerns could be prevented by better communication.
  - b. Another contributor to the high level of concern expressed may have been the fear that certain public health programs were going to be devalued relative to other programs. This is a cautionary experience to any group that attempts to prioritize among diverse public health activities based on imperfect or incomplete science. If this exercise had resulted in redirection of resources from one program to another I am certain the outcry would have been even stronger. I hope that those considering making budgetary decisions around "goals management" are taking note.

Report for the Internal Review Committee on "Actual Causes of Death in the United States" - James A. Mercy, September 22, 2004

My recommendations and comments are organized around three different themes: the clearance process, the content of the manuscript, and future research. In general, I believe that the authors made a legitimate and important contribution by updating the seminal article by McGinnis and Foege (JAMA 1993;270:2207-2212). I have two general concerns, however, about the process and their contribution. First, given the broad and important policy implications of this paper, I am concerned that there may have been insufficient attention given to legitimate criticisms and suggestions made by other CIOs and staff internal to the NCCDPHP. The authors were under some political pressure to get this paper out, but, in hindsight, I believe the paper and its message would have been enhanced by a fuller and more careful consideration of this input. Most importantly,

however, had such careful consideration been given perhaps CDC would not appear to be divided (As noted in Science 2004;304:804) about the research methods and conclusions included in this update. Second, given the complexity of this issue and its important policy implications I believe the comment section of the paper does not fully inform the reader about the limitations and various caveats that should be considered in interpreting the results of this update. More specific comments are as follows:

#### The Clearance Process:

This paper appears to have adhered to CDC's clearance policy, although there remains a question about whether one of the study authors was an author at the time she signed off on this paper in her role as a clearing official. Nevertheless there are several areas of concern raised by the clearance process for this manuscript that may influence CDC clearance policies and procedures:

1. It was difficult to track the timing and nature of some of the responses to the request for cross-clearance and the subsequent responses to revisions submitted back to CIOs by the authors that addressed the CIO concerns. This suggests that there may be a need to put in place some sort of tracking system so that the cross-clearance process can be well documented.
2. The concern raised above about the role of a clearing official who is also an author should be clearly addressed in the new CDC clearance policy. It might be helpful to add language under section E of the new policy that indicates that clearance officials should designate a staff member at an equal or higher organizational level to act in their capacity as a clearance official when they are an author or co-author on a manuscript or document that they are responsible for clearing.
3. There seems to be some confusion about what CDC policy was at the time this manuscript went through clearance concerning the process that should occur when a CIO chooses not to cross-clear a manuscript. The authors stated that the CDC policy at this time was that if a CIO chooses not to cross-clear a manuscript then, once a revision addressing the concerns raised by the CIO is sent back to the CIO, the CIO then has 4 weeks to respond. And then, if they fail to respond in 4 weeks, the authors can assume that the CIO has tacitly approved the manuscript for cross-clearance. The new CDC clearance policy does not speak to this issue. It might be wise to devise a clear policy for handling these situations in order to eliminate any confusion about this aspect of the process. This issue is particularly important because issues of cross-clearance may take on much greater significance as the silos inhibiting collaboration across CIOs become less significant.
4. The clearance policy within NCCDPHP requires that only an information copy of a manuscript be sent to divisions, outside the one within which the manuscript is cleared, whose subject matter is addressed within a manuscript. While this appears appropriate it appears that differences of opinion within NCCDPHP regarding the research methods and interpretations of the results were not sufficiently resolved prior to the manuscript being officially cleared and sent to

JAMA for review. In the new CDC clearance policy the CIO is given the responsibility of developing a process for resolution of disputes arising during clearance (See section B). In hindsight it may have been appropriate for the NCCDPHP ADS Office to have played a stronger role in resolving differences of opinion within NCCDPHP regarding this manuscript. It might be wise for CIOs to take seriously the need to develop a process which can help to resolve disputes such as these rather than institute requirements for intra-CIO cross-clearance that add complexity and time to this process.

#### The Content of the Manuscript:

My comments and concerns regarding the content of the manuscript are broken down in two parts. The first are concerns that may require that the authors issue an erratum to JAMA to correct errors in fact or method and the second are more general concerns about the manuscript that don't necessarily require any action, but I feel compelled to note.

#### *Potential Errors*

1. There may have been factual errors in the calculation of the overweight-attributable deaths in the manuscript. The figures used for the % of individuals in the U.S. who were not overweight in the U.S. (i.e., did not engage in the risk behavior in question) and the number of deaths used in the formula to calculate attributable fractions may have been in error. This issue should be resolved. Regardless of their ultimate impact on the number of deaths attributable to overweight if the figures used were in error an erratum should be issued with the correct calculations.
2. The authors may have incorrectly used the attributable-fraction formula in the calculation of overweight-attributable deaths by using adjusted relative risks in a version of this formula only appropriate for unadjusted relative risks. The knowledge about inappropriate use of adjusted relative risks in certain attributable-fraction formulas was in the literature prior to the preparation of this manuscript and was apparently shared with the authors prior to publication. If the attributable-risk formula was indeed miss-applied then the appropriate corrections should be made and an erratum should be issued that includes the necessary revisions.
3. The authors state that overweight accounts for the major impact of poor diet and physical inactivity on mortality. They cite Blair and Nichaman (Mayo Clin Proc 2002;77:109-113) in support of this contention. There are several potential problems with this contention. First, in a letter to JAMA responding to the authors, Blair, LaMonte, and Nichaman (JAMA 2004;291(24):2942) contend that their paper does not support this contention. Second, some NCCDPHP scientists believe that the current science base is not sufficiently robust to disentangle the causal connections and pathways to mortality involving these risk factors. I'm not certain whether or not the weight of evidence regarding this debate is clear enough to suggest that the statement in the manuscript should be withdrawn. Nor

am I entirely clear about how the authors themselves respond to this issue. It would be useful to have a written statement from the authors about their perspective on the scientific evidence supporting this contention.

#### *General Concerns*

1. One of the issues raised in discussions with NCCDPHP staff is that since the methods differ for calculating the number of deaths attributable to some of the "actual causes" between the McGinnis and Foege (JAMA 1993;270:2207-2212) paper and the update that making statements about trends in the paper is of questionable validity. In regard to deaths attributable to diet and physical inactivity, the authors pointed out that they felt confident doing this because the Allison et al. (JAMA 1999;282:1530-1538) paper, on which they based their method of calculating overweight-attributable deaths, came to a very similar estimate to McGinnis and Foege about the number of deaths attributable to this cause during a similar time period. Consequently with respect to deaths attributable to diet and physical inactivity the authors felt confident that their statement about the trend in these deaths was reasonable. The paper, however, does not make this logic clear to the reader. In hindsight it would have been very helpful to more clearly articulate the rationale used by the authors to justify making statements about these trends.
2. In general, and in my opinion, the comment section of the manuscript could have done a better job of articulating both the complexities of calculating the health burden attributable to specific causes and the limitations of the methods used. This may, in part, be explained by space constraints imposed by JAMA, but if these complexities and limitations had been more clearly acknowledged in the context of the author's stated purpose of updating McGinnis and Foege, the author's critics may have been less empowered in their response to this article. In regard to the complexities of calculating health burden of specific causes I don't believe sufficient attention was given to the fact that different general approaches could yield different results regarding the relative importance of "actual causes." For example, an approach based on years of potential life lost or one that also takes into account the impact of actual causes on morbidity could lead to conclusions that are different than those drawn from this study. As a consequence I believe it is important in a paper like this to acknowledge that the approach used is but one of several approaches and that premature mortality and morbidity are important dimensions of health burden that should be factored into the information needed to help formulate policy directions. In addition, not all of the limitations of the methods used were clearly articulated. For example, the fact that widely different methods were used to estimate mortality associated with the "actual causes" was not clearly pointed out. Again, in hindsight, acknowledging the difference in methodological approaches may have muted some critics and helped to emphasize that this paper was an update of McGinnis and Foege rather than a "state of the art" attempt to estimate the health burden associated with these "actual causes."



3. While a peripheral issue to the debate over the methods used to estimate the number of deaths attributable to diet and physical inactivity, the approach taken to estimate the number of deaths attributable to motor vehicles and firearms (and perhaps other "actual causes") is fraught with conceptual problems in my opinion. First, motor vehicles and firearms are deemed as actual causes, but considering these factors as actual causes in the same way that smoking or diet and physical inactivity are actual causes seems to represent a substantial oversimplification of the dynamics of these problems. Neither motor vehicles nor firearms are health risk behaviors or even health conditions. Both are generally considered to be mortality outcomes in much the same way as deaths associated with cancer or heart disease. Both are associated with numerous health risk behaviors. In the case of motor vehicle-related deaths this includes alcohol use, speeding, and the use of seat belts, for example. In the case of firearm-related deaths this includes access to firearms, violent behavior, and mental health problems such as depression, for example. The conclusion that 29,000 deaths in 2000 are attributable to firearms leads to potentially very erroneous interpretations. If one interprets this conclusion in a similar way to the results for smoking and diet and physical inactivity one might surmise that eliminating firearms in 2000 would have saved 29,000 lives, but this fails to account for the fact that those who would have used firearms to commit suicide or homicide may have chosen other methods to successfully complete their acts. The way this issue was handled in this manuscript has important political implications for CDC as well. This problem was pointed out to the authors during cross-clearance, however, no attempt was made to address it in revisions of the manuscript.
4. This is more in the category of wishful thinking, but, much in the same vein as their comment on genetics, it would have also been useful and important I believe for the authors to have pointed out in their comment section that there are other potentially important actual causes, not considered by them or McGinnis and Foegle, that may also make a substantial contribution to mortality. This would include adverse childhood exposures such as child maltreatment. In this case, although the science would not support the development of estimates on the impact of these exposures on mortality, the voluminous literature on the impact of these exposures on a broad range of health risk behaviors, mental health problems and morbidity suggests that this is an important area for further consideration.

#### Future Research:

I have one suggestion specific to the "Actual causes..." paper and three others that address the need to set the stage for more and better research on health burden at CDC. The issue of estimating the contribution of "actual causes" and to health burden is a critical one for CDC. Even the estimation of the health burden associated with specific categories of ill health is a complicated, but absolutely essential role for CDC. The need to generate these types of estimates has taken center stage, for example, in helping to define priorities and goals for the Futures initiative at CDC. The problem we constantly face in these efforts is that the data needed to generate these estimates is not uniformly available across the many domains of health that

CDC addresses: Areas where there has been substantial investment in public health research and surveillance systems are better able to document these burdens than those with less investment.

1. In regard to the "Actual causes..." paper I would recommend that an effort be made to write a "state of the art" paper on the health burden associated with smoking and diet and physical activity using comparable and alternative methods of calculating the associated health burden (e.g., mortality, YPLL, DALY, etc.). Such a paper would help to more clearly resolve the central debate over the "Actual causes..." paper and see if the conclusions that were reached are sensitive to alternative approaches to calculating health burden. I also suggest that the focus of this paper be on smoking and diet and physical activity alone and that other "actual causes" be left for other manuscripts. In the end these other causes are a distraction from the main issue of this paper and the underlying data and methods used to calculate burden for these other causes is so divergent that it may be impossible, at this time, to treat them in a way that is even near to being comparable.
2. As to more broad directions I suggest that CDC develop a common vocabulary for the terms and methods used in estimating health burden. The Actual Causes manuscript provides an example of the need for greater clarity and consistency in the vocabulary we use. The term "actual causes," in my opinion, suffers from a lack of conceptual clarity that leads to it being applied to different "causes" in ways that seem arbitrary and inconsistent as mentioned above in respect to motor vehicle-related and firearm-related deaths. Similarly organizing and defining the various methods useful for calculating health burden along with their strengths and limitations, if this hasn't already been done, would be of enormous value to many areas within and outside of CDC.
3. It might also be helpful to elevate attention to the methods of calculating health burden to a similar level and in a similar way to what CDC has done with the methods of prevention effectiveness and economic evaluation. These methods are so critically important to what we do at CDC and measuring our progress that an effort to help articulate, disseminate, and more broadly implement excellence in the application of these methods would be valuable across CDC. Even though many of the methodological building blocks for these methods are rooted in traditional epidemiology they have evolved in ways that go beyond, I believe, the typical training that an epidemiologist receives or has received in the past (e.g., the calculation of DALYs).
4. I would also suggest that future work on the health burden associated with "actual causes" should expand beyond our traditional conceptualizations of what these "actual causes" are. The literature on adverse childhood exposures such as maltreatment, as mentioned above, suggests that these exposures may even underlie or cause, to some extent, "actual causes" such as smoking and obesity.

Comments on process for Leading Causes of Death  
David Atkins, AIIRQ

General comments:



After hearing all the criticisms and the responses, I am left with the following observations:

- Pending review of the spreadsheet calculations, none of the concerns raised merit grounds for withdrawing the paper. The paper would have benefited from additional qualifications (e.g. range of estimates is underemphasized) and more cautious tone about the reliability of their estimates. The major limitations that might have led to overestimates of obesity deaths are discussed in one sentence after a series of less significant limitations.
- Like the McGinnis paper before it, such exercises have more elements of uncertainty than certainty. The reliability of any single estimate in this calculation (or in the earlier paper) can rightly be questioned. Nonetheless, I personally think the McGinnis paper served a useful purpose and the desire to update it was reasonable. The picture of the trends over the last decade seems reasonable even if the exact numbers are uncertain. That said, I think we should agree from this point forward to bury this model and its inherent weaknesses for good and strive to develop a more robust approach that could be used to estimate different causes of death in a consistent way. For policy purposes this could be used for both national and state estimates. Individual centers could build on the approaches taken by OSH to come up with methods that would be both scientifically rigorous and more suitable for comparisons across causes.
- The purpose of this paper was not conveyed adequately to the staff scientists. It would have been difficult to address all of their objections and still follow the overall approach of the earlier paper. Nonetheless, the perception by scientific staff that their valid concerns were ignored no doubt contributed to the controversy.
- The implication that obesity accounts for the vast majority of the effects of diet and physical activity doesn't appear justified. The conclusions, however, appropriately emphasize physical activity and diet as the appropriate targets of action.

#### Specific concerns raised:

1. Potential error in calculations of deaths caused by obesity: A possible inadvertent error in the calculation was raised based on the value of P0 and total number of deaths used. Recommendation: The authors should verify that the P0 and deaths for year 2000 are appropriate. The authors should share their spreadsheets with staff raising this concern so that the calculations can be independently verified (Steve: I don't think we raised the point with the authors that there was only 90% agreement with the calculations for obesity deaths looking at individual studies). Any errors discovered would require being addressed with an erratum note.

2. Use of inappropriate referent population (for P0): (i.e. should it be the population BMI 23-25 or all < 25). The authors note that they were simply updating the analysis of Adison who it seems used as P0 the group 23-25, and that they calculated it both ways without large differences noted. I think the appropriate referent population is that which was used in the cohort studies for calculating the RIR, which appears to have been the

approach used by the authors. This would exclude from the analysis excess deaths occurring in the group who are underweight, which are most likely to be confounded by illnesses that may have caused underweight. Including the underweight cohort with the optimal weight group would artificially raise the mortality in the referent group and reduce the risk of overweight. Note: I would like an epidemiologist to verify what one due with the prevalence of the underweight subgroup.

3. Applying adjusted RR to unadjusted population prevalence data is incorrect and results in upward bias in deaths due to obesity: This appears to be a problem carried over from the Allison analysis. The authors used this analysis because it produced estimates comparable to the McGinnis analysis with 1990 data. For purposes of describing trends over the last 10 years, this appears reasonable but should have been more clearly explained in the paper. Given that this constituted an important change from the McGinnis methodology, I would have suggested the 1990 estimates for deaths due to diet and PA be amended with the exact numbers from Allison's analysis using 1990 data rather than using the M&F numbers based on entirely different methods. This is only way for the change from 1990 to 2000 to be meaningful (Note: this is a new observation).

The effects of using age/gender specific risk estimates as is done for smoking is unclear but should be estimated in a sensitivity analysis (this may be what is done in the paper undergoing clearance). I think there can still be legitimate scientific arguments about the meaning of the attenuation in risk with age - is it real or the result of greater confounding due to underlying illness - and this should be the subject of the future conference.

4. Direct comparisons of deaths attributable to different causes is inappropriate due to variety of methods used (e.g. all cause mortality for obesity vs. cause specific for smoking; effect of adjusted vs. unadjusted estimates). This is the most legitimate concern to me. I don't believe such comparisons were the primary aim of the authors but are inevitable when precise estimates are given in a table, and this was certainly highlighted in the media reports. Given the uncertainties in the data, it is difficult to conclude that obesity is now equal to smoking or will shortly overtake it but the conclusion that smoking, diet and physical activity are the leading issues seems sound, especially as the later two are trending in the wrong direction. I would like to see the results of the RTI analysis that took a cause-specific approach using diabetes, heart disease and cancer as a way of validating the general conclusions.

5. Uncertainty around the data are not addressed: The tables and conclusions are less qualified than the original McGinnis estimates. Intrinsic limitations in the data could lead to underestimates and overestimates. The conclusion in the paper would have been more appropriate with greater qualifications regarding the exact estimates and increases.

6. The statement that obesity mediates most of the effects of poor diet and physical inactivity is incorrect: I agree with this criticism. There are strong effects of diet independent of effect on obesity, most notably adverse effects of saturated/trans fats on CVD and protective effects of diets high in fruits/vegetables/fiber on both CVD and

cancer. The argument for using obesity as a proxy are practical rather than scientific: it is far easier to define and measure than diet or physical activity and it build on growing concerns about rising obesity in the US. Due to confounding from the independent effects of diet/physical inactivity, however, it is likely to inflate the deaths attributable to obesity while ignoring deaths attributable to independent effects of diet and PA. This does not undermine the general conclusion of the paper – that diet and physical activity are comparable to smoking as leading public health issues. It could have unintended consequences for policy if it diverts attention to weight loss as the end in itself, rather than promotion of a healthy diet and activity. This question is a critical one for a future conference.

#### Recommended steps:

The authors should share the spreadsheet models (not just printouts) with scientists who have raised concerns to verify whether results are replicable and free of inadvertent errors. Any errors should be addressed in an erratum.

A sensitivity analysis should address possible effects of 1) using age and gender specific risk estimates for obesity comparable to those for tobacco. The analysis should also examine whether the population from which the risk estimates were derived is comparable to that of the US population – specifically, did these cohorts include sufficient numbers of patients above 75 to justify including deaths occurring in that age group.

A conference should be convened to specifically address methodological issues in estimating health effects of obesity. Issues to be addressed include dealing with confounding by diet/PA and other behaviors; effects and meaning of interactions with age and how to deal with it; estimating morbidity effects of obesity; lag time of obesity effects; using cause-specific deaths rather than overall mortality attributable to obesity; feasibility of estimating contribution of physical inactivity and poor diet rather than obesity.

The CDC should commit to produce a model that would improve on the approach taken by McGinnis and by Mokdad to produce individual estimates for specific behaviors that are more robust and comparable, and which could be applied to state data using BRFSS and state mortality data. The model might also incorporate estimates of the gains from likely changes in behavior (e.g., a 5% reduction in smoking prevalence vs. a 5% reduction in obesity).

I have mixed feelings about posting the model on the Web. It would be good for transparency but think it has enough problems that I don't think CDC should promote it as the optimal approach at present. If it is posted, it should be with a note that it is intended to give approximations of causes of death and that a number of issues may affect the reliability of any specific estimate.

Comments on CDC internal review of recent publication

*Actual Causes of Death in the United States, 2000*, JAMA, 291:1238-1245

Rachel Ballard-Barbashi, Associate Director, Applied Research Program, DCCPS, NCI  
October 1, 2004

As a committee member representing the National Institutes of Health, I was asked to comment in four areas:

- Whether the methodology used for the analysis was appropriate and reflected the best scientific methods available at the time of publication
- Whether a sensitivity analysis can assess the impact of model assumptions on the findings
- Whether the clearance process adhered to standard CDC practice and, specifically, if the internal policy for manuscript clearance was followed
- Whether a new methodology has become available since the publication that would better estimate the actual causes of death

I will address each point. However, based on this review, reviewing the literature and discussing this issue with many experts, my overall perspective is that the most important outcome of the debate engendered by this paper is to stimulate much more focused attention to improving the methodology for this field. Holding workshops and other forums and providing support for further research into the development of statistical methodology and required data resources are approaches to advancing the methodology. It is also important that efforts be made to disseminate information about the most current methodologies and their appropriate application for diverse purposes. CDC's plans to hold a workshop in this arena is a good idea. Given the research efforts at NCI, AHRQ and other DHHS agencies in this field, it would be good if this workshop could be developed as a cross agency effort. Planning the workshop as a cross agency effort may require more time and potentially delay the workshop. However, it would facilitate the discussion involving a broader group of experts, generally a benefit in such a complex field.

Point 1: Whether the methodology used for the analysis was appropriate and reflected the best scientific methods available at the time of publication.

In any scientific study, the methodology used is based on the purpose and timing of the study. In the case of this study, the authors intended to replicate a 1993 analysis by McGinnis and Foegle that estimated cause of death based on 1990 mortality data. They also decided to use methods from a 1999 study by Allison on causes of death as a source for data on relative risk estimates for all cause mortality. These two decisions drove the selection of methods. However, as one would expect, in the last 10 years, there have been a number of publications in this field that identified problems with some of the specific approaches of earlier methods. Several of the major issues that pertain to this publication are summarized below.

*Use of cause specific versus all cause mortality as the outcome evaluated*

In the 2004 publication by Mokdad et al, all cause mortality was used for examine cause of death for several risk factors, specifically for obesity, and cause specific mortality was used for others, such as tobacco. The advantage of using cause specific is that risk factors relate differently to disease outcomes and having estimates based on a specific set of causes may have more utility in determining priorities for reducing cause specific mortality. However, these analyses are very complex as data may be limited on all of the adverse and beneficial effects on cause specific mortality. Use of all cause mortality has the potential for providing an integrated measure of effect. A problem with the Mokdad et al analysis was that cause specific mortality was used in some cases and all cause mortality in others. While this was noted in the methods section of the paper, it was not be noted in the table, which was the primary summary used by casual readers and the press. This led to the comparison of very different mortality outcomes across these different risk factors. While perhaps not the intent of the authors, it was a common error in comparison made by readers.

*Need to use age and sex-specific estimates for relative risks from and prevalence of risk factors for inputs into the models*

For most of the risk factors examined, there is fairly extensive evidence that both relative risks of mortality from and prevalence of the risk factors varies by age and sex. Many recent analyses have used age and sex specific estimates in calculating mortality effects. While the effect of using these more discrete estimates may vary by disease outcome, as in the case of obesity and mortality as noted in two papers by Flegal et al (APPH 2004, AJE 2004), it is likely that these estimates will result in reducing the population attributable fraction of all cause mortality related to obesity.

*Limited discussion in the publication about the uncertainty of the estimates.*

It is likely that the word limit of JAMA precluded the authors from discussing many relevant issues in depth. The authors did acknowledge that the estimates were rough approximations and provide ranges for some estimates. Their approach in doing so largely reflected the approach used in the McGinnis and Foege paper and does not reflect more contemporary approaches to providing either confidence intervals or doing sensitivity analyses about a point estimate. In addition, table 2 in the paper provided only a comparison between the estimates in 1990 and 2000 and did not provide the confidence intervals about those estimates. It is common practice in medical and science journals today to require that confidence intervals be provided even within tabular summaries of data. Therefore, one might question why JAMA did not require such confidence intervals. Because casual readers tend to focus on tabular summaries, it is likely many readers had a mis-impression of the range about these estimates.

*Direct comparison across causes of death is likely invalid*

Because of the different approaches used to estimate cause of death by the different risk factors in the Mokdad et al paper, it is clear that direct comparison across causes of death is not particularly valid. In addition, there may be interaction between different risk factors related to mortality and morbidity where a portion of the population attributable fraction from one risk factor may be also related to another. The authors refer to this



point briefly in the discussion but did not undertake what would have been a very methodologically complex analysis to address these issues. It was not addressed within the McGinnis and Foege analysis on which the Mokdad et al analysis was based. This area requires much more extensive data resources and development of statistical methodology before progress can be made on this topic.

*Can obesity be used as the major surrogate of poor diet and physical inactivity?*

It is commonly accepted in the scientific community that characteristics of diet (at present only the characteristic of excess calories is widely accepted) and physical inactivity are major contributors to obesity at the individual level. However, the premise used in this paper and the original analysis by McGinnis and Foege, that obesity is the major modulator for the adverse effects of poor diet and physical inactivity on mortality is not supported by most population level evidence. Many studies for multiple different disease outcomes have demonstrated that the effect of both diet and physical activity are independent of the effect of BMI or various measures of body size or fat distribution. Therefore, it is not appropriate to claim that obesity is the major surrogate for the effects of poor diet and physical inactivity. In addition, obesity is likely to have effects on mortality outcomes that are independent of the effects of poor diet and physical inactivity.

Given these points, it is valid and, in fact, essential, that research efforts examine the effects of these three risk factors separately. At this point in time we have much more precise data on weight and height either from self report or from measured weight and height than we have in the areas of diet and physical activity. Therefore, we should consider the effects of obesity to be those of obesity and work to enhance data resources and methods for evaluating the separate effects of diet and physical activity.

**Point 2: Whether a sensitivity analysis can assess the impact of model assumptions on the findings**

A number of methodologic approaches have been developed to examine the impact of model assumptions on the precision of point estimates. The simplest of these is the calculation of confidence intervals. The more complex include various approaches to sensitivity analyses. This is an area that would benefit greatly to be included as a key issue in future workshops and research efforts. However, in addition to developing and using more sophisticated methods for estimating uncertainty, there is also a need to develop much clearer simple communication approaches to summarizing such uncertainty both within scientific papers as well as in lay communication media. Some approaches include showing the range about a point estimate through shading or other graphical techniques as is done in some sensitivity analyses. The field of health communication research should be challenged to take this on as a research issue.

**Point 3: Whether the clearance process adhered to standard CDC practice and, specifically, if the internal policy for manuscript clearance was followed**

I will not comment on the clearance process in any detail except to note that it appears as though the authors made a good faith effort to obtain input in the clearance process. Written details of exact response to each reviewer's comment were not provided so I cannot comment on whether CDC reviewers' comments were addressed. However, it



appears that final comments were not sent by reviewers within the 30 day period of review leading to individual phone calls to request final statements of clearance. It appears that these phone conversations provided informal statements of clearance. I cannot comment if that process adheres to the CDC standard procedures. Such information is best obtained from CDC staff who are very familiar with the CDC process.

Point 4: Whether a new methodology has become available since the publication that would better estimate the actual causes of death

My comments in response to the first point about issues in estimating cause of death clearly indicate that there are many methodologic issues that were not addressed in this publication that replicated an approach published in 1993. This would be entirely expected when replicating older methodologies. As I noted at the outset, I think the major benefit of this debate will be to focus HHS energies in this area to facilitate discussion among experts in the field of key research needs and subsequently to provide research support to further develop the resources needed and encourage further research in this area. This review has clarified that we should no longer be using the relatively simple methodology of the model used by several of these previous papers (McGinnis and Foege 1993, Allison et al 1999, Mokdad et al 2004).

The following is a brief listing of some of the key areas that would benefit from ongoing discussion and research.

- Examine the effect on PAR estimates of using cause specific vs all cause mortality for various risk factors
- Consider how to incorporate measures beyond mortality (morbidity, years of potential life lost, etc) into PAR estimates to obtain more comprehensive estimates of the effect of specific risk factors
- Examine how adjustment for a number of factors, such as interaction among risk factors and confounding, affects PAR estimates
- Consider which models are best suited for which subsequent uses of PAR estimates
- Quantify the degree of uncertainty about PAR estimates
- Support research to identify simple but valid approaches for presenting summary estimates in this area. This would also include communication research to better define how such approaches are understood by various audiences including lay, policy and scientific audiences.
- Support research and data resources to facilitate PAR estimates for diet and physical activity independently of using weight and height data as a measure of diet and physical activity.
- Support research to evaluate the differential effect of using difference referent points (i.e. for obesity the effect of using a BMI of 23-23 rather than <25) for estimating PAR. It is clear that for some outcomes, such as obesity, this referent point may have different effects in different populations defined by age, race or some other measures.

A few final points:

I understand there has been some discussion of putting the model that was used in the Mokdad et al analysis up on the CDC web site to facilitate other investigators utilizing the model. I would not recommend that approach but rather focus energies on supporting further development of these models. If consensus can be reached on which models are best used for which purposes following the planned workshop and further research, then it may be appropriate to provide several models with clear information about how they might best be used. While there is not one model appropriate to all needs it should be possible to reach consensus on some key characteristics on scientifically valid models at this point in time.

Finally, some specific errors in calculation were identified in this review process. It is appropriate that those errors be described and revised estimates be provided in an *erratum* which I understand is being developed by Dr. Mokdad. I do not have specific suggestions for any other corrections or clarifications to be included in such an *erratum*.

Recommendations on "Actual Causes of Death, 2000" Mokdad, Marks, Stroup, and Gerberding. JAMA 2004;291(10):1238-1245

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**Summary of the problem:** In the March 10 issue of JAMA, "Actual Causes of Death in the United States, 2000", authored by Ali Mokdad, James Marks, Donna Stroup, and Julie Gerberding, was published. The objective of the Mokdad et al paper was to update a previously published JAMA paper by McGuinnis and Foege wherein behavioral risk factors were identified and quantified as ultimately responsible for mortality; using published associations available at the time of the analysis, the McGuinnis and Foege paper concluded that approximately half of all 1990 deaths could be ascribed to one of their examined factors. The updated analysis was done, in part perhaps as a charge from outside of CDC, given that the prevalence of the risk factors as well as possibly the underlying associations had changed over the ten year period. A paper by Allison et al calculating obesity deaths using similar methods encouraged the idea. However, despite an attempt to couple the McGuinnis and Allison methodology, both presumably vetted, the Mokdad paper received substantial criticism. This critique might be summarized as follows: 1) the use of obesity as the single marker for diet and physical activity; 2) methods to attribute deaths due to obesity differ from those for other causes, particularly smoking, making comparisons invalid; 3) methods used to calculate deaths due to obesity were incorrect, and possibly the calculations used were done incorrectly; 4) not enough discussion of the robustness of the estimates; and 5) break-down in the clearance process that allowed the concern to go unaddressed within CDC.

My general conclusion is that the Mokdad et al paper makes some bold statements, bolder than the original McGuinnis and Foege paper, which might have been better off being presented as a policy exercise rather than a scientific study; the estimates seemed a combination of scientific calculation and expert opinion. Furthermore, the scientific reviewers of the paper who mentioned the problems were not taken as seriously as they could have been.

The following specific comments fall into four areas, as requested of the committee: 1) methodology; 2) sensitivity analysis; 3) clearance process; and 4) recommendations for future estimates.

#### I. METHODOLOGY

1. Use of obesity as a marker for diet and physical activity. The use of indicators in public health has a long history. Although the public health implications for addressing

obesity would likely center around diet and physical activity, the side-effects of focusing on weight loss could lose the attention of many non-obese with poor diet and activity habits. Regardless, in this case more explicit justification in the Methods was needed that the association between obesity and mortality could approximate the association between diet/physical activity and mortality. Inasmuch as CDC scientists dispute this assumption, the justification is even more important. (As someone who has little expertise in this area, the linkage of "lack of essential nutrients" to obesity seems weak.) Furthermore, the 15,000 deaths attributed among the (presumed) non-obese seemingly pulled from the hat is incongruous following the more rigorous exercise for obesity.

- a) What could have been done: Although I think a more careful explanation of the rationale in the Methods would have helped, though it could be that the scientific evidence does not support the use of this indicator for diet and physical activity. Closer collaboration with CDC and non-CDC experts to develop better estimates and indicators was warranted given the high profile of the risk factor. Alternatively, inferences could have been limited to obesity.
2. Methods used to attribute deaths due to smoking differ from methods for other causes, such as obesity, making comparisons among the causes biased. This is a valid criticism. Indeed, the McGinnis paper states more clearly up front, as well as in the tabled results, that the data are from a variety of sources with varying approaches to the calculations.
  - a) What could have been done: More sensitivity analysis could have been done and either incorporated into the Results or the Discussion section (see below). Starting up front the limitations of making comparisons from estimates based on differing methods and degrees of rigor would have helped as well.
3. Methods used to calculate number of deaths due to obesity were incorrect and possibly miscalculated. Differences between target population and study population. The use of the improper formula is a rather serious mistake to make. At the time this study was being conducted, the scientific literature had several papers describing potential bias. Following Allison et al in using an incorrect method was not justified. From the cross-clearance, it seems as if this bias from the wrong formula was pointed out to the authors. Given the sensitivity of the numbers of deaths to relatively small changes in the RRs, and the use of a handful of studies to obtain the numbers of deaths, as well as the averaging and rounding, and the addition of the 15,000, the actual effect of the wrong formula for the number presented in the table might or might not be small.
  - a) What could have been done: If the proper formula could not be used for some reason, more sensitivity analysis could have been done and either incorporated into the Results or the Discussion section (see below). Even without that effort, an explicit acknowledgment of the biases and sensitivity associated with the AR methods (including the sensitivity to changes in the RRs as well as interaction and confounding, potential bias between study and target populations, and the use of different formulas) might have softened the criticism.
  - b) Recommendation: Stated methods should be checked again. If the incorrect numbers were used in the spreadsheet calculations or the incorrect reference group was used, and the results are changed materially after the averaging and rounding and addition of 15,000, then an erratum should be submitted.

- c) Recommendation: Sensitivity analysis should be done to understand some of the effects of the methodological assumptions on the inferences.
  - d) Recommendation: If possible, the proper formula should be used to calculate the deaths attributed to obesity. If using the published assumptions but the more suitable equation leads to different estimates, an erratum could be submitted. Errata for this error have been published before (Mahn, Epidemiology 1996).
4. Stability of numbers of deaths overstated, or not understated sufficiently. This contributes to a sense of sureness that would likely not stand up to variance calculations and a fuller sensitivity analysis. Double counting is mentioned clearly in the Discussion section but not in the Introduction and not clearly in the Methods; indeed, for table readers, a reasonable conclusion would be that motor vehicle deaths had increased whereas the text opens with a sentence commending public health efforts in motor vehicle safety. Statements like "decreased" are not statistically supported; for alcohol deaths, given the wide range of estimates and the "best estimate" nature of the number presented, claiming a "decline" of 1.5% is a far reaching conclusion.
- a) What could have been done? A wider table could have included plausible ranges and data sources. More discussion in the Introduction and Methods about the imprecision of the estimates. The footnote in the Table should have mentioned the multiple counting so that readers would not automatically add the counts. Statements about decreasing numbers should have explicitly mentioned caveats or not have been made.
  - b) Recommendation: An expanded table could be put on the CDC web page.
5. Other observations. Sloppy comparisons were made: for sexual behavior, for example, comparing HIV deaths among all age groups in 2000 to those among those 13 or older in 1990, while likely reasonably accurate is not very scientific without some acknowledgement of the different populations.

## II. SENSITIVITY ANALYSIS

A sensitivity analysis would have helped the authors direct critique of the paper to the impact of some of the assumptions and methodological notes on the inferences. Several issues have been raised and mentioned above that would lend themselves to a sensitivity analysis: comparability across causes, both reported and "actual" causes of death; applying RR from study populations to target populations, particularly to an older population; interactions and confounding of RR estimates, etc....

- 1. Recommendation: Sensitivity analyses should be conducted carefully with the assistance of subject-matter specialists at CDC rather than simply quickly. The content of such an analysis could be determined from this committee. Depending on the findings, results could be made available online as a CDC report. In the future, if this sort of comparison is deemed important for policy, the content of appropriate sensitivity analysis could be discussed at the conference alluded to at the meeting on 20 September.

### III. CLEARANCE PROCESS

The clearance process appeared to have been begun in good faith, though given the dissent, it veered off the path. This likely happened since the Director is a co-author and presumably approved the paper. I think if the scientists had believed that their concerns were being considered, the issue of clearance may not have arisen.

1. What could have been done? When it became clear that there was dispute over clearance for some CIOs, an arbitrator should have been identified to the authors and the cross-clearance ADSs.
2. Recommendation. Although the clearance procedures are unambiguous about handling disputes, it is less clear about the proper channel when the Director is an author. It should be explicit in the procedures the clearance path when the Director and other senior staff are authors. In fact, extra care should be taken when the Director is an author to maintain the reputation of CDC, perhaps requiring signatures of more than one ADS.
3. Recommendation. As when responding to reviewers' comments in the journal publication process, written response to the specific comments of the cross-clearing ADSs should have been done rather than verbal understandings. The clearance procedure could include an optional request for written responses to comments.
4. Recommendation. It might be useful to have a mechanism for the senior ADS at CDC to hear petitions from scientists outside the official clearance process: like the Supreme Court, the ADS could choose to arbitrate the dispute or not.

### IV. SUMMARY RECOMMENDATION

1. Current paper. If a thorough sensitivity analysis can be performed, verified, and cleared appropriately within a reasonable time frame, then a supporting document describing such results could be posted on the web. Anything short may be inconclusive. Given the controversy, the content of the analysis should be agreed upon between the authors and an outside source, such as this committee.
2. Future.
  - a. Estimation based on best educated guesses should be acknowledged as such up front; for this paper the experience of the authors supports their ability to make some decisions with weak data, though some decisions may ultimately be incorrect.
  - b. If these types of estimates are deemed to be important for policy decisions then the work should be divided loosely into two groups: 1) the senior scientists, such as Mokdad and colleagues, who decide on the causes to be examined, how to present the results, the necessary statistical analyses, and conclusions, and 2) the subject-experts who perform the actual calculations for the estimates and have input into the comparisons. The conference on this topic could determine that the scientific concerns outweigh the policy needs and decide to put efforts into other ways to convey this sort of information.
  - c. In general, published papers need not contain cumbersome detail, however, supporting work should be available upon request that addresses potential concerns about bias; this would allow users of the numbers to obtain a fuller

grasp of their underpinnings, CDC could begin or revive an online working paper series to house such documents.

- d. Simplified methodologies could be developed and made available to states wishing to replicate the results using comparable methods, but the limitations of both the methods and the simplified methods should be explicitly defined. If this is not feasible, allocating resources for CDC staff to produce state-specific estimates could be considered.